REMARKS

The title has been amended more accurately to reflect the nature of the invention.

The applicant maintains his view that the claims of the present invention are not obvious over the claims of US Patent 6,627,659. The Examiner is correct ion stating that the specification may be used as a dictionary to interpret the claims contained in the same application. However, what the examiner is doing is to use the present specification to construe a different document. Even if N-actylcysteine is acting as a prodrug in the method described in US 6627659, the burden is on the examiner to show this. The examiner refers to the Akuri article for this purpose. This article, however, was not published until 2007, long after the claimed priority date of December 19, 2003 and so is not evidence of the state of the art at the relevant date. As ponted out in response to the previous office action and supported by documents published closer to the relevant date than the Akuri article, those skilled in the art did not regard acteylcysteine administered orally as required by the present claims as a pro drug for cysteine.

Nevertheless, in order to try to expedite prosecution of the present application, the applicant is filing a terminal disclaimer of the term of any patent granted on the present application which extends beyond the statutory term of US Patent 6,627,659.

Turning now to the rejection under 35 USC 103, this again relies on the assumption that what applies to N-acetyl cysteine wold also apply to cysteine.

The examiner refers to two passages in Lucatelli. Although these are not fully identified, they seem to be the following:

Page 1272 - Conclusions paragraph:

It is important to consider oxidative stress as a **potentially** important source of patient morbidity and mortality, although this knowledge is **not yet immediately**

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applicable in the clinical arena. **Further** well-designed, randomized controlled clinical **trials** with anti-oxidants (e.g. vitamin E, vitamin C, N-acetyl cysteine, L-arginine) **are required** to establish evidence based recommendations for clinical practice. (Emphasis added)

Page 1274 right hand column.

Therefore, the estimation of the anti-oxidant status of CRI patients comprises the measurement of the different compounds of the anti-oxidative system in plasma and cells. Despite the lack of standards and conflicting results, the determination of plasma and cells. Despite the lack of standards and conflicting results, the determination of plasma levels of vitamin C and GSH-Px, and the erythrocyte content of SOD, GSH, GSH-Px and vitamin E has been applied successfully, revealing anti-oxidant deficiency in CRI.

and lower down in the column:

Haemodialysis (HD) may induce repetitive bouts of oxidative stress, primarily through membrrane bio-incompatibility and endotoxin challenge. While alterations in pro- and anti-oxidant capacity start in the early stages of CRI, they are most pronounced in patients on dialysis. Overall, however, there is some controversy as to whether the onset of regular dialysis improves or worsens oxidative stress.

In addition to the passages referred to by the examiner, note should also be taken of the first paragraph in the section "Anti-oxidant defence systems" on page 1274 which points out that anti-oxidant systems are present naturally and counteract free radicals. It points to Table 1 as setting out such systems.. Neither N-acetyl cysteine nor cysteine is mentioned.

Since the paper is a consensus paper seeking to set out what is agreed upon in the

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field, these conclusions are important they include agreement that oxidative stress appears to play a crucial role in pathogenesis in end stage renal disease (ESRD) including dialysis-related amyloidosis and includes the following as means fore reducing oxidative stress:

> As oxidative stress and inflammation appear to be important in pathogenesis of CVD in ESRD patients, anti-oxidant treatment strategies could be beneficial.
>
> Although anti-oxidant therapy with vitamin E and C has not shown to reduce cardiovascular risk in the general population, the increased level of oxidative stress in CRI patients makes it an attractive approach; a recent study in dialysis patients points in this direction, but further well-designed clinical trials are recommended.
>
> The reduction in dialysis-induced mechanisms by biocompatible membranes and ultrapure dialysis fluids is desirable.

From these comments, it is clear that at the time of the paper, there was some thought that use of antioxidants, although not helpful in the general population, might be beneficial in patients with CRI as a result of oxidative stress that they suffer, but by no means clear that this was tied in any way to dialysis, where as noted above "there is some controversy as to whether the onset of regular dialysis improves or worsens oxidative stress" . This is therefore not a teaching to administer antioxidants of any type to patients specifically in combination with their hemodialysis treatment. Furthermore, apart from the suggestion that further information is necessary to establish a proper theory relating to oxidative stress in ESRD in general and that testing with N-acetyl cysteine might give results relevant to formulation of such a theory, apart from the cryptic reference to Tepel's work, there is no mention of either cysteine or N-acetyl cysteine anywhere in the document.

It is submitted that Locatelli therefore does not contain any teaching to administer antioxidants in conjunction with hemodialysis. At most it suggests that this is a field for

further study.

Dröge adds nothing relevant to this. It teaches that patients having a cysteine deficiency may beneficially be treated with a cysteine source that is capable of being transported across the cellular membrane and includes N-acetyl cysteine in the list of compounds that may act as this source. Cysteine itself is not listed. (See column 2 lines 30 - 35). The examiner comments that"a reasonable interpretation of Dröge's teachings is that administration of cysteine is not excluded.' It is respectfully submitted that this is not a reasonable interpretation of Dröge. Where it is taught that the objective is to raise the levels of a compound in a cell and the list of compounds given as being capable of doing this excludes the compound itself, one has to believe that the exclusion was deliberate. As pointed out in some detail in response to the previous action, cysteine and N-acetyl cysteine have different pharmacological properties. The examiner cannot therefore just assume that cysteine itself would be a suitable "cysteine source for Dröge's purposes when Dröge himself does not say so. As pointed out previously, Droge is seeking to insert cysteine into liposome lumens so that it can result in an increase of the thiol level in blood plasma. Nothing in this suggests that cysteine itself should be used for this.

This is confirmed by the fact that Locatelli suggests vitamin E, vitamin C, and L-arginine as suitable compounds for testing along with N-acetyl cysteine. Had he thought cysteine had the same properties it seems unlikely that he would have omitted it.. N-acetyl cysteine is well known as an antioxidant. Although cysteine has antioxidant properties, there is no reason to think that it could be substituted for N-acetyl cysteine in any particular specific situation. *A fortiori* there is no reason to think that one skilled in the art would have thought that the anti-oxidant studies suggested by Lucatelli should be carried out with cysteine in order to investigate the mechanism more fully and even if this were not the case, there is no reason to tie any treatment specifically to acts of hemodialysis..

It is therefore submitted that the requirements of 35 USC 103 have been complied

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with and that this application should be allowed.

Respectfully submitted,

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